

## PTAC meeting held 12 & 13 November 2009

### (minutes for web publishing)

PTAC minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not necessarily a complete record of the PTAC meeting; only the relevant portions of the minutes relating to PTAC discussions about an application that contain a recommendation are published.

PTAC may:

- (a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- (b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- (c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

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## 1 Minutes of PTAC Meeting Held August 2009

- 1.1 The Committee reviewed the record of the PTAC meeting held on 13 & 14 August 2009 and made the following minor amendments:
- 1.1.1 Clopidogrel – paragraph 1.14: replace “The Committee noted that previously it had recommended” with “The Committee noted that it had previously recommended”.
  - 1.1.2 Cox-2 Inhibitors – paragraph 2.2: replace “The Committee recommended that a COX-2 inhibitor is listed” with “The Committee recommended that a COX-2 inhibitor be listed”.
  - 1.1.3 Riluzole (Rilutek) – paragraph 5.8: replace “abnormal liver function tests (LFTs) occur in 10% of patients which necessitates monitoring of LFTs” with “abnormal liver function tests (LFTs) occur in 10% of patients which necessitates monitoring”.

## 2 Subcommittee Minutes

- 2.1 Cancer Treatments Subcommittee minutes – 25 June 2009
- 2.1.1 The Committee considered CaTSoP’s recommendation to fund nilotinib for chronic myeloid leukaemia if cost neutral, or as a third line treatment. The Committee **reiterated its previous recommendation** to decline the application to list nilotinib on the Pharmaceutical Schedule.
  - 2.1.2 The Committee noted and accepted the remainder of the record of the Subcommittee meeting.

## 3 Varenicline (Champix) Special Authority Criteria for Smoking Cessation

- 3.1 The Committee considered the varenicline (Champix) Special Authority and recommended the following changes to the Special Authority (changes in bold):

Varenicline – initial treatment using the starter pack (box containing 11 tablets 0.5 mg and 14 tablets 1 mg) and the 14 day continuation pack (box containing 28 tablets 1 mg)

- 1. Commencement of short-term therapy as an aid to achieving abstinence in a patient who has indicated that they are ready to cease smoking; and,

2. The patient is part of, or about to enrol in, a comprehensive support and counselling smoking cessation programme which includes prescriber or nurse monitoring (details of the program must be specified in the Special Authority application); and,
3. The patient has failed to quit smoking using other smoking cessation treatments including NRT and **either** nortriptyline **or** bupropion; and,
4. The patient has not used varenicline in the last 12 months; and,
5. Varenicline is not to be used in combination with other **pharmacological** smoking cessation treatments and the patient has agreed to this; and,
6. The patient is not pregnant; and,
7. The patient is not under the age of 18 years; and,
8. The patient has consented to follow-up questions regarding the effects of their varenicline treatment (contact details must be specified in the Special Authority application).

## 4 Clopidogrel for Aspirin Intolerance and Acute Coronary Syndrome

### Application

- 4.1 The Committee considered whether clopidogrel should be funded for patients with stroke, TIA or coronary events who cannot tolerate aspirin, and reviewed the evidence provided in the CURE trial (Yusuf et al. 2001: NEJM: 345 (7). pp. 494-502) with respect to extending access for acute coronary syndrome beyond three months.

### Recommendation

- 4.2 The Committee **recommended** that the aspirin allergy definition in the clopidogrel Special Authority is amended with a high priority as follows (changes in bold):

Note: Aspirin allergy is defined as a history of anaphylaxis, urticaria or asthma within 4 hours of ingestion of aspirin, other salicylates or NSAIDs; **or aspirin intolerance is defined as those with intolerable gastrointestinal side-effects due to aspirin use in spite of proton pump inhibitor therapy.**

The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;*

- 4.3 The Committee considered that its previous **recommendation** of a low priority to extending clopidogrel therapy to twelve months for acute coronary syndrome/revascularisation procedure was appropriate.

### Discussion

- 4.4 **The use of clopidogrel for patients with stroke, TIA or coronary events who are aspirin intolerant.**
- 4.5 The Committee noted it had previously discussed the use of clopidogrel in aspirin intolerant patients at its August 2009 meeting.
- 4.6 The Committee noted that clopidogrel is funded for patients with stroke, TIA or coronary events if they are aspirin allergic but not if they are aspirin intolerant.
- 4.7 The Committee considered that aspirin plus a proton pump inhibitor is appropriate for patients with stroke, TIA or coronary events who are aspirin intolerant. The Committee considered that if a patient was still intolerant despite the use of a proton pump inhibitor then clopidogrel monotherapy was appropriate.
- 4.8 The Committee considered that dipyridamole monotherapy was not an appropriate alternative to aspirin for aspirin intolerant patients due to a lack of evidence. The Committee noted a Cochrane Review (De Schryver et al. 2007: Cochrane Database of Systematic Reviews, Issue 3) which concluded that dipyridamole monotherapy had no effect, irrespective of the dose, on vascular death in patients who presented with arterial vascular disease; and that while a reduction in the risk of vascular events occurred following cerebral ischaemia a dose of at least 400 mg of dipyridamole was required.
- 4.9 The Committee recommended that the aspirin allergy definition in the clopidogrel Special Authority is amended with a high priority as follows (changes in bold):
- Note: Aspirin allergy is defined as a history of anaphylaxis, urticaria or asthma within 4 hours of ingestion of aspirin, other salicylates or NSAIDs; **or aspirin intolerance is defined as those with intolerable gastrointestinal side-effects due to aspirin use in spite of proton pump inhibitor therapy.**
- 4.10 **Acute coronary syndrome**
- 4.11 The Committee reviewed the evidence provided in the CURE trial (Yusuf et al. 2001: NEJM: 345 (7). pp. 494-502) with respect to extending access for acute coronary syndrome beyond the current three months.
- 4.12 The Committee noted it had previously discussed the use of clopidogrel in acute coronary syndrome/revascularisation at its August 2009 meeting.
- 4.13 The Committee noted that International Guidelines (ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction) indicated that clopidogrel could be used in addition to aspirin for up to twelve months in patients with acute coronary syndrome.
- 4.14 The Committee noted that the CURE trial investigated the effect of three to 12 months of clopidogrel plus aspirin therapy, versus aspirin monotherapy, in preventing additional cardiovascular events in patients with acute coronary syndrome.
- 4.15 The Committee noted that while follow-up assessments with the patients occurred at one, three, six, nine and twelve months, the three months data was not provided; nor

was there any statistical analysis performed using it. The Committee noted that the analyses that were presented were limited to the one and twelve month data sets.

- 4.16 The Committee noted that the analyses performed were not well described and that cumulative hazard plots were presented, rather than survival curves. The Committee considered that it was not clear as to whether the cumulative hazard plots included the three, six and nine month data or whether a best-fit curve had been fitted to the one and 12 month data, thus limiting the usefulness of any divergence in the cumulative hazard plots.
- 4.17 The Committee noted that the period of clopidogrel treatment for the patients in the trial varied between three and twelve months. The Committee therefore considered that the only conclusions that could be drawn from the trial were that the addition of clopidogrel to aspirin provided a benefit over aspirin alone, and that the duration of clopidogrel therapy should be between three and 12 months.
- 4.18 The Committee recommended that the CUA be based on the absolute risk reduction of events between one and 12 months. The Committee felt that the best estimate over the study period could be achieved by plotting a straight line between one and 12 month data points.
- 4.19 The Committee considered it unlikely that relevant new data would become available.
- 4.20 The Committee considered that its previous recommendation of a low priority to extending clopidogrel therapy to twelve months for acute coronary syndrome/revascularisation procedure was appropriate.

## **5 Rivaroxaban (Xarelto) for Venous Thromboembolism (VTE) Prophylaxis**

### **Application**

- 5.1 The Committee reviewed an application from Bayer New Zealand Ltd for the listing of rivaroxaban (Xarelto) on the Pharmaceutical Schedule for the treatment of venous thromboembolism prophylaxis after major orthopaedic surgery.

### **Recommendation**

- 5.2 The Committee **recommended** that rivaroxaban for the treatment of venous thromboembolism prophylaxis after major orthopaedic surgery be listed in the Pharmaceutical Schedule with a medium priority.

The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

## Discussion

- 5.3 The Committee reviewed an application from Bayer New Zealand Ltd for the listing of rivaroxaban (Xarelto) on the Pharmaceutical Schedule for venous thromboembolism prophylaxis after major orthopaedic surgery.
- 5.4 The Committee noted the RECORD 1 (Study Number 11354 report, Eriksson et al. 2007: Eriksson et al. 2008: NEJM: 358 (26). pp. 2765-2775), RECORD 2 (Study Number 11357 report, Kakkar et al. 2007), RECORD 3 (Study Number 11356 report, Lassen et al 2007: Lassen et al. 2008: NEJM: 358 (26). pp. 2776-2786), and RECORD 4 (Study Number 11355 report, Turpie et al. 2008 report) trials which compared rivaroxaban with enoxaparin for the prevention of venous thromboembolism after total hip replacement or total knee replacement using various treatment regimes. The Committee considered that the quality of the trials was very good and that they indicated that rivaroxaban was perhaps slightly more efficacious than enoxaparin in preventing venous thromboembolism following total hip replacement and total knee replacement, but that it also had a slightly larger increase in the risk of major bleeding.
- 5.5 The Committee noted the conclusions and recommendations of NICE (April 2009), the Scottish Medicines Consortium (November 2008), CEDAC (November 2008) and NPS RADAR (August 2009).
- 5.6 The Committee considered that the most appropriate comparator to rivaroxaban, that is currently subsidised, is low molecular weight heparin as this was the comparator used in the clinical trials; however, the Committee noted that aspirin and warfarin might be used in clinical practice in New Zealand.
- 5.7 The Committee considered that rivaroxaban had the same or similar clinical effect as enoxaparin and dabigatran and that these three products could be listed in the same therapeutic subgroup for the purposes of reference pricing.
- 5.8 The Committee considered that PHARMAC staff should seek the opinion of orthopaedic surgeons to determine current practice, and the place in therapy, if any, they considered rivaroxaban would occupy.
- 5.9 The Committee considered that if rivaroxaban was listed then it should be restricted via Special Authority to a daily dose of 10 mg for the prophylaxis of venous thromboembolism following total hip replacement (up to five weeks) or total knee replacement (up to two weeks). The Committee considered that if this restriction was not applied it would be likely that rivaroxaban would be used for acute coronary syndrome and atrial fibrillation as an alternative to warfarin, even though it is not registered for these indications.
- 5.10 The Committee noted that the supplier's estimates of the rate of Post Thrombotic Syndrome and the cost and proportion of home visits to administer enoxaparin were reasonable.
- 5.11 The Committee noted that the entry of generic enoxaparin would reduce the cost-effectiveness of rivaroxaban.

- 5.12 The Committee considered that, for patient convenience and to improve compliance, it would be appropriate for patients to receive a full course when they are discharged from hospital.

## 6 Etravirine (Intelence), Antiretroviral for HIV

### Application

- 6.1 The Committee reviewed an application from Janssen-Cilag Pty Limited for the funding of etravirine (Intelence) on the Pharmaceutical Schedule for the treatment of patients with Multi- Drug Resistant (MDR) Human Immunodeficiency Virus (HIV).

### Recommendation

- 6.2 The Committee **recommended** that the application for etravirine for the treatment of MDR HIV be deferred until darunavir was listed on the Pharmaceutical Schedule
- 6.3 The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals;*

### Discussion

- 6.4 The Committee noted that etravirine was a diarylpyrimidine (DAPY) derivative non-nucleoside reverse transcriptase inhibitor (NNRTI) used in the treatment of MDR HIV. The Committee noted that etravirine had a resistance profile different from currently funded NNRTIs due to its ability to bind reverse transcriptase in multiple conformational distinct modes and thereby escapes the effects of mutation that lead to drug resistance. Members noted that the most common first generation NNRTIs mutation K103N did not confer virological resistance to etravirine.
- 6.5 The Committee noted two randomised, double-blind, placebo control phase III trials, DUET I and II studies, provided by the supplier relevant to etravirine's safety and efficacy. Members noted that both studies evaluated etravirine in combination with darunavir and optimised NRTI with or without enfuvirtide. Members considered the trials to be of good quality.
- 6.6 The Committee noted 24 week pooled data showed 58.9% of the etravirine group achieved a viral load below 50 copies per ml compared to 41.1% of the placebo group. Members noted unpublished poster presentations which showed durability of response at 48 weeks 61% etravirine versus 40% placebo under 50 copies per ml and 96 weeks 57% etravirine versus 36% placebo under 50 copies per ml.
- 6.7 The Committee noted safety data to 96 weeks in the Duet pooled data showed no major safety concerns. Members noted the incidence of rash was 7.5% in the etravirine group versus 2.6% in the placebo group. Members noted that rash was usually of grade one or two severity.

- 6.8 The Committee considered there was an unmet clinical need for patients with MDR HIV. The Committee noted that addition of a single agent to a failing regime is likely to fail rapidly, and that etravirine was probably the third choice for antiretrovirals in this setting as there is some cross resistance from earlier NNRTIs.
- 6.9 The Committee considered that all evidence for etravirine was in combination for the currently unfunded protease inhibitor darunavir and as such etravirine should not be considered for funding until darunavir was funded.

## 7 Budesonide/Eformoterol (Symbicort Turbuhaler) for Asthma

### Application

- 7.1 The Committee reviewed an application from AstraZeneca for the widening of access to budesonide with eformoterol powder for inhalation (Symbicort Turbuhaler) for asthma.

### Recommendation

- 7.2 The Committee **recommended** that access be widened to budesonide with eformoterol powder for inhalation to allow use as single inhaler therapy. The Committee assigned a low priority to this recommendation.
- 7.3 The Committee **recommended** that the application be referred to the Respiratory Subcommittee for review.
- 7.4 The Committee **recommended** that the Special Authority restriction for all combination ICS/LABA inhalers be amended so that the inhaled corticosteroid threshold matched that in the Prescribing Guidelines for Inhaled Long-Acting Beta-Adrenoceptor Agonists.
- 7.5 The Decision Criteria relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

### Discussion

- 7.6 The Committee considered that the application was supported by large studies of good quality that appeared to have reasonable consistency of effect. It was felt by the Committee that the generalisability of these large trials to the clinical use of single inhaler therapy is a key question which was not answered completely by the application.

- 7.7 The Committee noted the results of a paper by Kuna et al (Int J Clin Pract. 2007 May;61(5):725-36), and noted that the exclusion criteria resulted in nearly one-quarter of enrolled patients being excluded from randomisation. In particular, members noted that patients who were infrequent users of reliever medication were excluded from the study during the run in period. Members considered that this group of patients would likely show less benefit from the single inhaler therapy regimen. Members noted that this limited generalisability to an important group of patients with asthma.
- 7.8 Members considered that there was other key comparators not included in the application e.g. separate LABA and ICS inhaler vs. SMART. There are also other single inhaler maintenance and relief combination inhalers such as the beclomethasone/salbutamol combination inhaler study programme by Papi et al (N Engl J Med 2007;356:2040-52) may also help to inform the discussion.
- 7.9 The Committee noted that the British Thoracic Society guidelines supported the use of single inhaler therapy with the caveat that “the total regular dose of inhaled corticosteroids should not be decreased”. Members noted that this would result in an increase in overall ICS doses if this strategy were adopted.
- 7.10 Members considered that, if the results of the presented studies were generalisable, it would be reasonable to expect a reduction in hospitalisations through the use of single inhaler therapy. However, members were concerned that it may result in greater self-management in some patients who may opt to increase dosing in preference to seeking medical advice.
- 7.11 The Committee noted that eformoterol is more closely related to fenoterol and isoprenaline than salmeterol. Members noted that excessive use of eformoterol can result in beta-adrenoceptor downregulation, and as such patients would be less likely to respond to rescue treatment.
- 7.12 The Committee considered that the proposed access may result in its use in step two of the GINA classification of asthma severity (mild persistent asthma) in place of short-acting beta-adrenoceptor agonists. Members noted that, if this was to occur, there would be a large financial implication of the increased use of LABAs in mild asthma.
- 7.13 The Committee considered the article published by Taylor et al (N Z Med J. 2008 Nov 7;121(1285):106-18.). This article was supportive of combined beta agonist and corticosteroid therapy but there were some unanswered issues about its use. The Committee felt that Respiratory Subcommittee could look into these issues in detail and make recommendation on use of combination inhalers.
- 7.14 The Committee noted that while single inhaler therapy was intended for use as one dose BD plus PRN, there was a reasonable risk that patients would use two doses BD plus PRN.
- 7.15 The Committee noted that the Special Authority restriction for combination ICS/LABA inhalers had a steroid threshold of 800 µg beclomethasone-equivalent. Members considered that this was inconsistent with the Prescribing Guideline for Inhaled Long-Acting Beta-Adrenoceptor Agonists.

## 8 Sunitinib (Sutent) for Advanced Renal Cell Carcinoma

### Application

- 8.1 The Committee reviewed an application from Pfizer for the listing of sunitinib (Sutent) for the treatment of advanced renal cell carcinoma (RCC).

### Recommendation

- 8.2 The Committee **recommended** that sunitinib be listed on the Pharmaceutical Schedule under Special Authority for the treatment of patients with advanced renal cell carcinoma as follows:

Special Authority for Subsidy

Initial application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for three months for applications meeting the following criteria:

All of the following:

- 1 The patient has advanced, inoperable, renal cell carcinoma; and
- 2 The patient is treatment naive; and
- 3 The patient has good performance status (WHO/ECOG grade 0-1); and
- 4 The disease is of predominant clear cell histology; and
- 5 The patient has good or intermediate prognosis as defined by NCCN Clinical practice guidelines for Kidney Cancer; and
- 6 Sunitinib to be used for a maximum of 2 cycles.

Renewal only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months where:

Both:

- 1 No evidence of disease progression; and
- 2 The treatment remains appropriate and the patient is benefiting from treatment.

Notes:

Sunitinib treatment should be stopped if disease progresses.

NCCN Clinical practice guidelines for Kidney Cancer note that predictors of short survival include, high blood lactate dehydrogenase (LDH) level (>1.5 times upper limit of normal), high blood calcium level (corrected Ca<sup>++</sup> >10 mg/dL or 2.5 mmol/L), anaemia, time of < 1 year from diagnosis to the need for systemic treatment, and low performance status (KPS <80%). Patients with none of these risk factors have good prognosis, those with 1 to 2 have intermediate prognosis, and those with 3 or more have poor prognosis. For more information see [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp)

- 8.3 The Committee gave this recommendation a low priority.
- 8.4 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; and (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (iv) The clinical benefits and risks of pharmaceuticals; and (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## Discussion

- 8.5 The Committee noted that this proposal had previously been considered by PTAC and CaTSoP and had been declined.
- 8.6 The Committee reiterated its view that current treatment options for advanced RCC were unsatisfactory.
- 8.7 The Committee noted that the supplier had provided further information, however, members considered that major evidence base for the use of sunitinib in renal cell carcinoma remained the A618-1034 study comparing sunitinib with interferon alpha, the final analysis of which had now been published (Motzer et al J Clin Oncol August 2009, 27:3584-3590).
- 8.8 The Committee noted that in the Motzer study median overall survival (OS), the pre-planned primary endpoint, was greater in the sunitinib group than in the interferon alpha group (26.4 v 21.8 months), however, this was not statistically significant (hazard ratio (HR) = 0.821; 95% CI, 0.673 to 1.001; P =0.051). Members noted that median progression-free survival was significantly longer in the sunitinib group as was objective response rate compared with interferon alpha. Members concluded that sunitinib was associated with a small benefit compared with interferon alpha treatment.
- 8.9 The Committee reviewed a report describing patient reported health-related quality-of-life (QOL) results from the Motzer trial (Cella et al J Clin Oncol August 2008 26:3763-3769). Members noted that the authors concluded that sunitinib provided superior QOL compared with interferon alpha treatment and that according to pre-established thresholds, the differences were clinically meaningful. However, members noted that the absolute differences in the main scores reported were very small (FKSI-15 difference was 3.27 (range 0-60) and FJSI-DRS difference was 1.98 (range 0-36). Members also noted that global quality of life, as measured by the EuroQOL EQ-5D, intersected after 10 cycles of treatment and that importantly, QOL data was provided for patients still on treatment, nothing is known about QOL after patients stopped treatment.
- 8.10 The Committee also reviewed a publication of data from an expanded access programme enrolling 4,564 patients across 52 countries (Gore et al Lancet Oncology, Vol. 10 No. 8 pp 757-763). Members noted that in this sunitinib open label expanded access program median progression-free survival was 10.9 months and overall survival was 18.4 months, both shorter than the results observed in patients enrolled in the Motzer study treated with sunitinib (PFS 11 months and OS 26.4 months). Members also noted that objective response rate for patients treated with sunitinib was significantly lower in the Gore study compared with the Motzer study (17% compared with 47%), however, members noted that in the Gore study response monitoring was not formalised.
- 8.11 The Committee recognised the lack of alternative treatment options in this disease, and thus their strong desire for an effective therapy to offer to patients. Members considered that sunitinib was a very high cost treatment given its moderate benefit compared with interferon alpha treatment and therefore considered that it should only be funded if the cost-effectiveness analysis and budget impact were acceptable to PHARMAC.

- 8.12 The Committee considered that, if funded, up to 80 patients per year would be eligible for treatment with sunitinib. Members noted that the supplier's patient estimates were too low as they were based on patients with first presentation of advanced RCC, and therefore, omitted patients presenting with relapsed advanced disease. Members noted that up to 30% of patients with resected disease would likely relapse within 3 years of surgery.
- 8.13 The Committee considered that sunitinib should be funded initially for two cycles, and treatment should be stopped at that point if disease had not responded. Members further considered that after that treatment should be stopped immediately on disease progression. Members considered that using these stopping rules 10-20% of patients would likely discontinue treatment after two cycles due to lack of response. Members further considered that the average total dose of sunitinib would be 12,397 mg based on the mean total dose observed in the Motzer study. Members noted that although the datasheet indicates that sunitinib is dosed at 50 mg per day for four weeks of a six week cycle some prescribers will likely use lower continuous dosing regimens.

## 9 Gemcitabine for Pancreatic Cancer

### Application

- 9.1 The Subcommittee considered further information regarding an application from the New Zealand Association of Cancer Specialists to widen access to gemcitabine to allow for its use as adjuvant treatment of macroscopically resected pancreatic cancer.

### Recommendation

- 9.2 The Committee **recommended** that the application be declined.
- 9.3 The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 9.4 The Committee noted that this proposal had previously been considered by PTAC and CaTSoP in February 2009 and both committees had recommended, based on the clinical evidence available at that time, that access to gemcitabine be widened to allow for its use as adjuvant treatment of macroscopically resected pancreatic cancer, with a high priority.
- 9.5 The Committee considered data from a new study (ESPAC-3 v2) presented at the American Society of Clinical Oncology meeting in June 2009. Members noted that

although the data had not yet been published in full, this large phase III study was particularly relevant to the application since it compared adjuvant treatment with 5 fluorouracil (5FU) or gemcitabine in patients with resected pancreatic cancer.

- 9.6 The Committee also considered further correspondence from the applicants regarding the ESPAC-3 v2 data and the updated cost-utility analysis undertaken by PHARMAC staff. Several recently published studies evaluating the efficacy of 5FU and/or gemcitabine in pancreatic cancer were also provided.
- 9.7 The Committee noted that ESPAC-3 (v2) was a randomised open-label, phase III trial of 1,088 patients with resected pancreatic ductal adenocarcinoma. Patients were randomised to receive either 5FU and folic acid (FA) (FA, 20 mg/m<sup>2</sup>, IV bolus injection followed by 5-FU, 425 mg/m<sup>2</sup>, IV bolus injection given on days 1–5 every 28 days (the Mayo regimen) or gemcitabine (1,000mg/m<sup>2</sup> IV infusion on day 1, 8 and 15 every four weeks) for six months. Members noted that at a median follow-up of 34 months there was no difference in survival between the two treatment groups with median survival for the 5FU treated patients of 23 months (95% CI: 21.1, 25.0) compared with 23.6 months (95%CI: 21.4, 26.4) for the gemcitabine treated patients.
- 9.8 The Committee considered that despite showing no efficacy benefit gemcitabine was associated with fewer toxicities compared with the 5FU/FA regimen used in the ESPAC-3 (v2) study. It was noted that more patients on 5FU experienced grade 3-4 diarrhoea compared with gemcitabine (13% in the 5FU/FA arm vs. 2% in the gemcitabine arm). However, members noted that currently in New Zealand oncologists did not use the Mayo 5FU/FA regimen, rather, in the colorectal cancer setting they routinely use weekly 5FU/FA which, according to the applicants, in the colorectal cancer setting is less toxic and more convenient to deliver compared with the Mayo regimen.
- 9.9 The Committee considered that although the currently used weekly 5FU/FA had not been properly evaluated in pancreatic cancer it was likely that its efficacy would be similar to that of the Mayo regimen used in the ESPAC-3 (v2) study given that in colorectal cancer it is accepted that there is comparable effectiveness across a range of various 5FU schedules, including weekly bolus 5FU/FA, protracted venous infusional 5FU, and capecitabine.
- 9.10 The Committee considered that gemcitabine would likely not offer any safety or efficacy benefit over a weekly 5FU/FA regimen in the adjuvant treatment of patients with resected pancreatic cancer. Members considered that given the lack of any meaningful benefit compared with current funded treatment options the additional cost of funding gemcitabine in the adjuvant setting could not be justified.

## **10 Olanzapine Depot Injection (Zyprexa Relprevv) for Schizophrenia and Related Psychoses**

### **Application**

- 10.1 PHARMAC staff sought advice from the Committee to help inform its cost-utility analysis (CUA) for olanzapine depot injection (Zyprexa Relprevv) for schizophrenia and related psychoses. The Committee noted that the funding application for olanzapine depot injection was made by Eli Lilly and was first reviewed by the Committee in May 2009.

### **Recommendation**

- 10.2 The Committee deferred making a recommendation on the application for olanzapine depot injection pending a CUA and updated budget impact analysis being performed by PHARMAC staff.

### **Discussion**

- 10.3 The Committee noted it had reviewed the application from Eli Lilly in May 2009 and had deferred making a recommendation on the application pending a CUA being performed by PHARMAC staff and a review of the application by the Mental Health Subcommittee of PTAC.
- 10.4 The Committee noted that the Mental Health Subcommittee had reviewed the application in July 2009 and had recommended that olanzapine depot injection be funded subject to similar Special Authority restrictions to risperidone depot injection, but with the added requirement for a trial of oral risperidone. The Subcommittee considered that, within the context of the mental health therapeutic area, this recommendation should be considered a medium-high priority.
- 10.5 The Committee noted that PHARMAC staff required further advice from PTAC to help inform its CUA, particularly around the evidence used to support differences in side effect profiles between risperidone depot injection and olanzapine depot injection.
- 10.6 The Committee considered that the questions relating to the differences in the side effect profiles of olanzapine depot injection and risperidone depot injection are difficult to answer due to limited data, noting that most of the available studies are relatively short-term whereas significant weight gain and extrapyramidal side effects from antipsychotic medications usually occur over several months or more. Further, as noted in a Cochrane review of trials comparing risperidone with olanzapine (Jayaram et al, Cochrane Database of Systematic Reviews 2006;2; Art. No.: CD005237. DOI: 10.1002/14651858.CD005237), adverse events were under-reported in many trials, some trials did not report on the incidence of weight gain, and some adverse events were only reported if they occurred in more than 5% or 10% of patients.
- 10.7 The Committee reiterated its previous view that the study populations are not completely representative of the patients that are likely to be placed on olanzapine depot injection in New Zealand, because in New Zealand approximately two thirds of patients receive depot antipsychotics as part of a Compulsory Treatment Order. The Committee considered that, as a result, patients on depot antipsychotics in New Zealand tend to

have higher co-morbidity and substance abuse rates. The Committee noted that a disproportionately high number of Maori and Pacific Island people are subject to a Compulsory Treatment Order and therefore will be more likely to be given depot injection treatments. The Committee considered that these factors are likely to increase the risk of patients in New Zealand developing extrapyramidal side effects and weight gain from depot antipsychotic medications compared with the populations studied in the clinical trials.

- 10.8 The Committee noted that the degree to which a side effect of medication is considered to be a reason to change medications varies depending on the patient and the treating clinician, and it was possible that in clinical practice antipsychotic medication may be more readily changed because of side effects than is reflected by the incidence of 'significant adverse events' or 'discontinuations' because of adverse events reported in clinical trials.
- 10.9 As an example, the Committee referred to a study comparing risperidone depot injection with olanzapine tablets in patients with schizophrenia (Keks et al, Br J Psychiatry 2007;191:131-139), where weight gain was considered a significant adverse event in 9% and 6% of patients on olanzapine and risperidone, respectively, yet 36% and 20% of patients on olanzapine and risperidone, respectively, gained over 7% of body weight over one year. The Committee considered that in many patients a 7% weight gain would be viewed as being clinically significant (for example because it could lead to compliance issues) and could lead to a change in treatment.
- 10.10 In the absence of better data, the Committee considered that it would be reasonable to use the adverse events data from the 12-week randomised phase of the above mentioned study by Keks et al (2007) to model differences in extrapyramidal side effects (including Parkinsonism) and weight gain in the CUA. The Committee considered that the long-term implications of side effects should also be modelled, particularly weight gain and extrapyramidal effects.
- 10.11 The Committee noted that the incidence of these side effects reported in other publications (Lieberman J et al, N Engl J Med 2005;353:1209-1223 and the 2006 Cochrane review cited above) followed the same general trends as in the Keks et al study.
- 10.12 The Committee considered that there was no clinical trial evidence to suggest that there was any difference in the incidence of sexual dysfunction between risperidone depot injection and olanzapine depot injection.
- 10.13 The Committee considered that the CUA should also consider the longer-term emergence of side effects and the model should extend beyond the timeframes of the clinical trials.
- 10.14 The Committee considered that the required three hour observation of patients following treatment with olanzapine depot injection should be included in the CUA, as in many cases this would need to be done by a health professional (e.g. a nurse), either at a clinic or in the patient's home.

## 11 Dornase Alpha for Cystic Fibrosis

### Application

- 11.1 The Committee considered an application from the Cystic Fibrosis Advisory Panel (the Panel) to amend the dornase alfa Special Authority criteria.

### Recommendation

- 11.2 The Committee **recommended** that the requirement for patients to have an FEV<sub>1</sub> less than 65% of predicted be removed.
- 11.3 The Committee further **recommended** that the application to amend the FEV<sub>1</sub> improvements at one month and six months be deferred pending further information from the Panel.
- 11.4 The Committee **recommended** that the requirement for one and six month reviews be retained in the criteria.
- 11.5 The Committee **recommended** that the requirement for sputum expectoration be removed from the criteria and that “ongoing respiratory infections in keeping with cystic fibrosis” be retained.

### Discussion

- 11.6 The Committee considered that the strength and quality of the evidence provided was of good quality. Members noted that a meta-analysis had been published and that this included RCTs comparing dornase alfa to placebo or hypertonic saline. Members considered that data coming through now is likely to be largely retrospective from treatment registers. Members noted that the evidence provided by the Panel emphasised the evidence for benefit in patients with milder lung disease.
- 11.7 The Committee considered that cystic fibrosis is predominantly a disease of Caucasians and that any inequalities for access to treatments were likely to be geographic. Members also noted that there were regional variations in predicted values used for spirometry which may affect eligibility for therapy.
- 11.8 The Committee considered that the FEV<sub>1</sub> standard deviation figures reported in the Fuchs study appeared to be a typographical error and that any decision that had been based on this data should be reviewed.
- 11.9 The Committee considered that any changes to health sector expenditure resulting from changes to the dornase alfa Special Authority criteria would largely be from direct treatment costs.
- 11.10 The Committee considered that benefit had been shown at all levels of lung function and that there was no reason to restrict dornase alfa to those with moderately impaired lung function. Members considered that it would be appropriate to initiate dornase alfa therapy earlier to prevent early decline of lung function.

- 11.11 The Committee considered that access should remain targeted with the requirement to show an objective response to therapy for funding to continue. Members considered that the requirement for one month and six month reviews should be retained in the criteria and considered that ongoing reviews may aid in compliance.
- 11.12 The Committee considered that it may be appropriate to amend the response requirements but were uncertain whether the required improvement in lung function was an absolute measure or a relative measure. The Committee deferred making a recommendation on the response parameters pending further information from the Panel.
- 11.13 The Committee noted that the Panel had recommended that a requirement for patients to have previously trialled hypertonic saline be included in the criteria. Members considered that this should be incorporated in to the criteria.
- 11.14 Members noted that European and US databases confirmed benefit from treatment and that earlier instigation of treatment led to better outcomes. The Committee considered that dornase alfa was now a standard of care globally.
- 11.15 The Committee noted the Panel's comments that international data comparisons would show worse outcomes in New Zealand patients. Members considered that international comparisons should be made with caution as clinical practice varies internationally and dornase alfa is one of many factors that determine outcomes.
- 11.16 The Committee noted that one study had shown that alternate day dornase alfa therapy provided similar benefits to daily treatment. Members considered that alternate day therapy could be investigated and that this might halve expenditure on dornase alfa. Members noted that this might actually reflect current practice, noting that PHARMAC's data suggests that average dornase alfa compliance is around 50-60 percent.
- 11.17 The Committee considered that patient numbers would increase if the Special Authority criteria for dornase alfa were relaxed, but that uptake would occur over a number of years.

## 12 Vildagliptin (Galvus) for Type 2 Diabetes

### Application

- 12.1 The Committee reviewed an application from Novartis New Zealand Limited for the funding of vildagliptin (Galvus) on the Pharmaceutical Schedule for the treatment of patients with type 2 diabetes.

### Recommendation

- 12.2 The Committee **recommended** that the application for vildagliptin for the treatment of patients with type 2 diabetes be declined.
- 12.3 The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v)*

*The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

## **Discussion**

- 12.4 The Committee noted that vildagliptin was a dipeptidyl peptidase (DPP-4) inhibitor used in the treatment of patients with type 2 diabetes. The Committee noted that this was the first application received for funding vildagliptin and that it had been considered by the Diabetes Subcommittee at its meeting in August 2009. Members noted the relevant record of the Diabetes Subcommittee meeting.
- 12.5 The Committee noted 14 phase III trials provided by the supplier relevant to vildagliptin's efficacy and safety. The Committee noted that the majority of studies were short in duration and that some pivotal studies had been omitted from the application, however the studies showed that vildagliptin was better than placebo for lowering HbA1c but was generally inferior to other active agents.
- 12.6 The Committee noted a recent systemic review and meta-analysis of major cardiovascular outcomes in trials of intensive therapy of type 2 diabetes (Ray KK et al; Lancet 2009; 373:1765-72) that had not been provided in the application. Members noted that this study concluded that for a pooled estimate change of 0.9% in HbA1c there were statistically significant reductions in non-fatal myocardial infarction, coronary heart disease event, however not for stroke or total mortality.
- 12.7 The Committee noted a Cochrane review (Richter B et al; Cochrane Database of Systemic Reviews 2008) that was more recent than the Amori review (Amori RE et al; JAMA 2007; 298:194-206) that had been considered by the Diabetes Subcommittee. The Committee noted that vildagliptin versus placebo (diet, activity and weight loss) decreased HbA1c by 0.6% (95% CI -0.7 to -0.5) over the period of the studies (majority being 24 weeks). The Committee noted that vildagliptin versus an active comparator increased HbA1c by 0.3% (95% CI 0.1 – 0.5) compared to the other active treatments.
- 12.8 The Committee considered, for the purposes of funding, that vildagliptin has the same or similar therapeutic effect as metformin, sulphonyureas, glitazones and acarbose.
- 12.9 The Committee considered that vildagliptin would be used in combination with metformin. The Committee considered that there was little evidence for its use in combination with sulphonyureas, glitazones or acarbose. The Committee considered that in clinical practice vildagliptin would be used as add in therapy in those not achieving response on a single agent and that this use would be widespread as so few of those with type 2 diabetes achieve good glycaemic control.
- 12.10 The Committee considered that the health risks of vildagliptin are largely unknown because of the short duration of the studies provided. The Committee noted that infection rates appear to be increased with sitagliptin, an alternative DPP-4 inhibitor, but not vildagliptin.
- 12.11 The Committee considered that patients with type 2 diabetes not achieving a HbA1c result of less than 7% could potentially be eligible for vildagliptin. Members considered that this could be as high as 65-75% of those with type 2 diabetes on oral therapy.

- 12.12 The Committee considered that the dose for vildagliptin would most likely be 100 mg daily.
- 12.13 The Committee noted that the supplier proposed no restriction on the funding of vildagliptin. The Committee considered that vildagliptin, if funded, should be restricted by Special Authority for those intolerant of metformin and sulphonyureas or in those who can tolerate metformin but are failing to meet HbA1c targets. The Committee noted that vildagliptin use together with sulphonyureas has not been demonstrated to be safe and that there is little evidence of combined use with glitazones.
- 12.14 The Committee considered that there may be additional health sector costs from unexpected adverse events given that these are still unknown. The Committee considered that more long-term safety data was necessary.

### **13 Sitagliptin (Januvia) and Sitagliptin and Metformin (Janumet) for Type 2 Diabetes**

#### **Application**

- 13.1 The Committee reviewed a re-application from Merck Sharpe and Dohme for the listing of sitagliptin (Januvia) and an initial application for its combination sitagliptin and metformin formulation (Janumet) on the Pharmaceutical Schedule for the treatment of patients with type 2 diabetes.

#### **Recommendation**

- 13.2 The Committee **recommended** that the application for sitagliptin (Januvia) and sitagliptin and metformin (Janumet) for the treatment of patients with type 2 diabetes be declined.
- 13.3 The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

#### **Discussion**

- 13.4 The Committee noted sitagliptin was first reviewed for funding in May 2008 and that the application was declined due to an unfavourable cost utility analysis and a lack of long-term data. The Committee noted that the application was forwarded to the Diabetes Subcommittee who reached similar conclusions.
- 13.5 The Committee noted that this was the first application received for funding sitagliptin and metformin in combination and that it and the re-application for sitagliptin had been considered by the Diabetes Subcommittee at its meeting in August 2009. Members noted the relevant record of the Diabetes Subcommittee meeting.

- 13.6 The Committee noted a 30 week extension study (Williams-Herman et al.; *Curr Med Res Opin* 2009; 25(3):569-583) of the original randomised controlled trial of sitagliptin alone or in combination with metformin in various doses. The Committee also noted a further extension to this study, in abstract form by Williams-Herman et al, with data out to two years in 402 patients. The Committee noted that glycosylated haemoglobin reductions were similar after two years and that 32% of patients on sitagliptin monotherapy achieved a HbA1c target of <7%, whereas 60% in the metformin 2,000 mg combination and 45% in the metformin 1,000 mg combination achieved this target. Members noted that in all treatment groups including metformin monotherapy, glycosylated haemoglobin reduction was greater for higher baseline HbA1c.
- 13.7 The Committee noted a randomised, placebo-controlled trial of sitagliptin added to glimepiride with or without metformin over 24 weeks (Hermansen et al. *Diabetes Obes Metab.* 2007 Sep;9(5):733-45). The Committee noted that at endpoint, the overall placebo-subtracted HbA1c reduction was 0.74%, with a reduction of 0.89% on glimepiride plus metformin versus 0.57% on glimepiride alone. Members noted that reductions in fasting plasma glucose, post-prandial glucose and increased HOMA- $\beta$  measurements were seen in the sitagliptin patients relative to placebo.
- 13.8 The Committee noted a pooled analysis of safety and tolerability of sitagliptin, up to two years in duration, covering 12 double-blind trials of 6,139 patients (3,415 given sitagliptin) (Williams-Herman et al.; *BMC Endocrine Disorders* 2008, 8:14). The Committee noted that the incidence rates of adverse events, serious adverse events (7%) and discontinuations (35%) were similar between sitagliptin and comparator groups. The Committee noted that nasopharyngitis was more common in the sitagliptin group, though not statistically significant. The Committee noted that the hypoglycaemia rate was higher in the non-exposed group, mainly where a sulphonylurea was in the comparator arm and that there were no differences in abnormal laboratory values between exposed and non-exposed groups.
- 13.9 The Committee noted a systematic review and meta-analysis on the efficacy and safety of incretin therapy in type 2 diabetes that was provided by PHARMAC (Amori et al; *JAMA.* 2007;298(2):194-206). The Committee noted that the weighted mean placebo-subtracted HbA1c difference in 2,404 patients from seven studies was -0.74% and the mean fasting plasma glucose was decreased by 1.2 mmol/l from baseline. The Committee noted that there was a small increase in weight of 0.52 kg but no change in lipid profile but there was an increased risk of infection, particularly urinary tract infection (relative risk 1.42) and a slightly greater incidence of headache.
- 13.10 The Committee noted a perspective by Nathan published in the *New England Journal of Medicine* in February 2007. In addition it also noted the *Drug and Therapeutics* bulletin published in July 2008.
- 13.11 The Committee considered that the quality of the evidence in the application was reasonable although the strength was limited. The Committee considered that the additional data from the supplier does show that the response to sitagliptin is durable up to two years, but appears slightly inferior to treatment with metformin alone. Members considered that the safety profile for sitagliptin from the studies provided seems reassuring, although patient exposure at two years is still limited. The Committee noted that in September the FDA issued a boxed warning following 88 cases of acute pancreatitis, some severe, most occurring within 3 months of onset of sitagliptin

exposure. Members noted that the pooled analysis by Williams-Herman et al. 2008 did not reveal any signs of pancreatitis.

- 13.12 The Committee considered that the addition of metformin as combination therapy offers only a modest benefit of 0.5% reduction in HbA1c over monotherapy. Members noted that a recent Prescrire International editorial advised against the use of sitagliptin and metformin in combination.
- 13.13 The Committee noted that the supplier had proposed special authority criteria for sitagliptin and sitagliptin and metformin similar to the previous pioglitazone special authority. Members considered that the supplier's estimate of patient numbers was likely to be an under-estimate unless tighter targeting mechanisms become available, particularly as glycosylated haemoglobin targets in national guidelines are now being lowered to 6.5%.
- 13.14 The Committee considered that there was no unmet clinical need for sitagliptin or sitagliptin and metformin in combination other than for intolerance to existing therapies.
- 13.15 The Committee noted that PHARMAC staff had estimated the cost per quality-adjusted life year (QALY) of sitagliptin to be greater than \$100,000. The Committee did not agree with the supplier's view that the cost-effectiveness analysis would be unlikely to be critical to a decision for the funding of sitagliptin and sitagliptin and metformin in combination.

## 14 Insulin glulisine (Apidra) for Diabetes Mellitus

### Application

- 14.1 The Committee reviewed an application from Sanofi Aventis Limited for the listing of insulin glulisine (Apidra) on the Pharmaceutical Schedule for the treatment of patients with type 1 and type 2 diabetes mellitus.

### Recommendation

- 14.2 The Committee recommended that there were no clinical reason not to fund insulin glulisine (Apidra), and further **recommended** that insulin glulisine for the treatment of patients with type 1 and type 2 diabetes mellitus only be listed on the Pharmaceutical Schedule if cost-neutral (or cost-saving) to the Pharmaceutical Schedule.
- 14.3 The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 14.4 The Committee noted that insulin glulisine, a human insulin analogue produced using recombinant DNA technology, is used in the treatment of patients with type 1 and type 2 diabetes mellitus. The Committee noted that this was the first application received for funding insulin glulisine and that it had been considered by the Diabetes Subcommittee at its meeting in August 2009. Members noted the relevant record of the Diabetes Subcommittee meeting.
- 14.5 The Committee noted that a large number of studies of various duration (12 hours to 26 weeks) and a good range of subjects (normal volunteers, patients with type 1 diabetes, patients with type 2 diabetes and different weight profiles) had been provided. However the Committee noted that the majority of these had been presented as abstracts and therefore were not considered. The Committee noted that in peer reviewed published studies insulin glulisine has been compared to regular human insulin and insulin lispro. Members noted that insulin glulisine had been compared to insulin aspart, however only one study had been provided where it was given as a continuous subcutaneous infusion and therefore was also not considered.
- 14.6 The Committee noted a 26 week study (Dailey et al.; Diabetes Care 2004; 27 2,363-68) in patients with type 2 diabetes who were randomised to receive either insulin glulisine or regular human insulin with both receiving insulin isophane as long-acting insulin. The Committee noted that the study showed significant reductions in HbA1c for both groups however insulin glulisine was significantly superior to regular human insulin. Members noted that there were no differences in insulin dose, hypoglycaemia, other adverse effects and in production of insulin antibodies.
- 14.7 The Committee noted a 26 week study (Dreyer et al.; Horm Metab Res 2005; 37:702-7) in patients with type 1 diabetes. The Committee noted that the study was a randomised parallel group study involving 339 patients who received insulin glulisine and 333 patients who received insulin lispro. The Committee noted that the results showed similar change in HbA1c with both insulins and the criteria for non-inferiority for insulin glulisine versus insulin lispro were met. The Committee noted that there were no differences in blood glucose profiles but insulin lispro patients required 1.82 units more insulin than insulin glulisine.
- 14.8 The Committee noted a 12 week study (Garg et al.; Endocrine Practise 2005; 11:11-17) in patients with type 1 diabetes who were either given insulin glulisine 0-15 minutes before meals or immediately after meals compared to regular human insulin administered 30-45 minutes before meals. The Committee noted that the pre-meal insulin glulisine patients received a significantly greater effect on HbA1c than the other two groups and also for blood glucose profiles. Members considered that overall there was little difference between the groups.
- 14.9 The Committee noted a single dose study (Heise et al.; Diabetes, Obesity and Metabolism 2007; 9:746-53) assessing the onset of action comparing insulin glulisine versus insulin lispro in non-diabetes subjects of differing body weight. The Committee considered that the results indicated that insulin glulisine had a faster-acting profile than insulin lispro.
- 14.10 The Committee noted a randomised, open label two arm crossover study in patients with type 2 diabetes with a short duration of 12 hours on each study day (Luzio et al.; Diabetes Research and Clinical Practice 2008; 79:269-75). Members noted that the

study compared the pharmacokinetics and dynamics of insulin glulisine versus insulin lispro and that overall the levels of glucose were almost identical. Members noted that the results showed a faster absorption rate for insulin glulisine than insulin lispro.

- 14.11 The Committee noted a study (Rayman et al.; Diabetes Research and Clinical Practice 2007; 76:304-312), which was of similar design as that by Dailey et al. The Committee noted that the results showed that there was no between treatment difference in endpoint HbA1c with changes of -0.32% for insulin glulisine and -0.35% for regular human insulin. The Committee noted that nocturnal hypoglycaemia was less frequent in the last two months of the study in the insulin glulisine group.
- 14.12 The Committee considered that there appeared to be a small benefit from the use of insulin glulisine versus regular human insulin, but no real difference when compared to insulin lispro. Members noted that the Diabetes Subcommittee had considered that there was little difference between insulin glulisine and insulin aspart.